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Health Effects Assessment for Fluorenes

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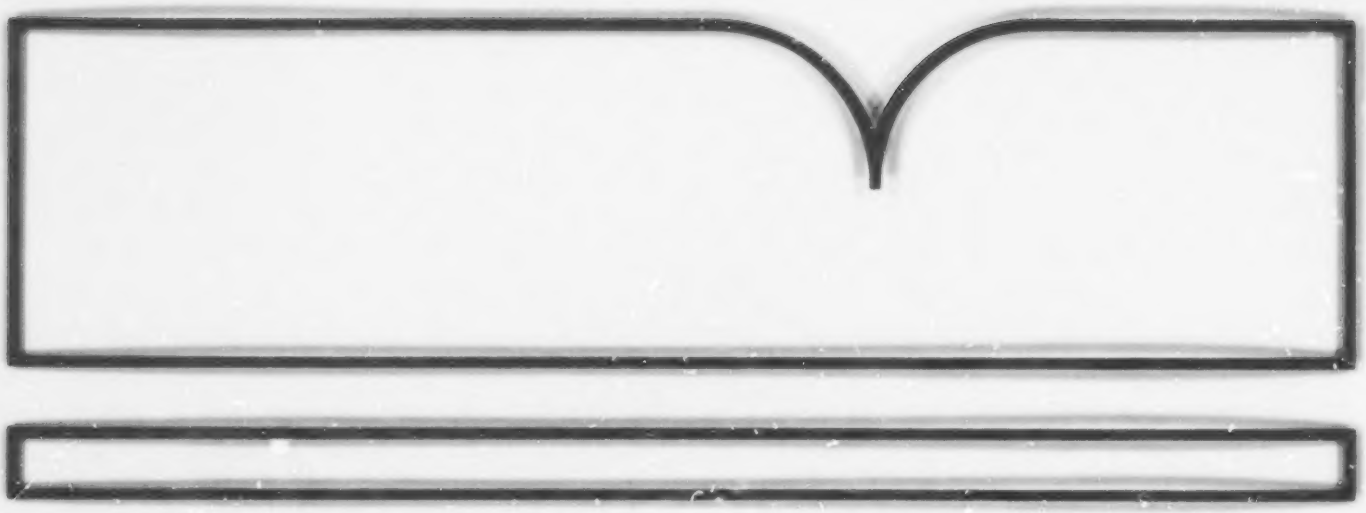

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HEALTH EFFECTS ASSESSMENT FOR FLUORENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with Fluorenes. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Fluoranthene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-049. NTIS PB81-117608.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Polynuclear Aromatic Hydrocarbons. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-069. NITS PB81-117806.

U.S. EPA. 1980c. Hazard Profile for Polynuclear Aromatic Hydrocarbons (PAH). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for Fluorene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for Fluoranthene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

ABSTRACT

Oral and inhalation toxicity data were not sufficient to derive risk assessment values for fluorene or benzo(j,k)fluorene. Short-term test data indicate that benzofluorene has the potential to be carcinogenic in humans. The available short-term data for fluorene, however is insufficient to address its carcinogenic potential.

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LIST OF ABBREVIATIONS

CHO	Chinese hamster ovary
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
HGPRT	Hypoxanthine-guanine phosphorbosyl transferase
RfD	Reference dose
RfD_S	Subchronic reference dose
SCE	Sister chromatid exchange

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and environmental fate of selected fluorenes are presented in Tables 1-1 and 1-2.

In both air and water, fluorene and benzo(j,k)fluorene are largely associated with particulate matter. When adsorbed to particulate matter, the fluorenes could potentially be transported long distances before ultimately being removed by chemical reaction or wet and dry deposition (HSDB, 1986). Vapor-phase fluoranthene has an estimated photodegradation half-life of 4-5 days (HSDB, 1986) and fluorene may have a similarly short reaction half-life. In water, the fluorenes should rapidly adsorb onto sediments and particulate matter in the water column and bioconcentrate in aquatic organisms. Physical properties indicate that adsorption and bioconcentration of benzo(j,k)fluorene should be greater than that of fluorene. The fluorenes are apparently stable in sediments for decades or more (Bjoerseth et al., 1979). In the unadsorbed state in water, benzo(j,k)fluorene is predicted to photodegrade (half-life days to weeks); unadsorbed fluorene may also photochemically degrade (HSDB, 1986; Sadtler, n.d.). The fluorenes are expected to adsorb strongly to soil and to biodegrade in the presence of acclimated microorganisms. Fluorene should degrade faster than benzo(j,k)fluorene (HSDB, 1986).

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Fluorene
(CAS 86-73-7)

Property	Value	Reference
Chemical class:	polynuclear aromatic hydrocarbon	
Molecular weight:	166.22	
Vapor pressure at 25°C:	6.6×10^{-4} mm Hg, estimated	Mackay and Shui, 1981
Water solubility at 25°C:	1.90 mg/ℓ	Mackay and Shui, 1981
Log octanol/water partition coefficient:	4.18	Hansch and Leo, 1985
Bioconcentration factor:	1290 (bluegill sunfish)	Veith et al., 1979
Soil adsorption coefficient:	3070	Lyman et al., 1982
Half-lives in Air:	NR	
Water:	NR years (adsorbed to sediments)	Bjoerseth et al., 1979
Soil:	NR	

NR = Not reported

TABLE 1-2

Selected Physical and Chemical Properties and
Half-Lives for Benzo(j,k)fluorene

Property	Value	Reference
Compound:	benzo(j,k)fluorene	
CAS number:	206-44-0	
Chemical class:	polynuclear aromatic hydrocarbon	
Molecular weight:	202.26	
Vapor pressure at 25°C:	1.91×10^{-3} mm Hg, estimated	Mackay and Shui, 1981
Water solubility at 25°C:	0.26 mg/ℓ	Mackay and Shui, 1981
Log octanol/water partition coefficient:	5.20	Hansch and Leo, 1985
Bioconcentration factor:	380 (rainbow trout) 3981 (fathead minnow)	NLM, 1986
Soil adsorption coefficent:	9160	Lyman et al., 1982
Half-lives in Air:	4-5 days (vapor phase)	NLM, 1986
Water:	days to weeks (unadsorbed state) years (adsorbed to sediments)	NLM, 1986 Bjoerseth et al., 1979
Soil:	NR	

NR = Not reported

Because fluorene and benzo(j,k)fluorene have been found in ambient air and water, exposure by inhalation and ingestion are of concern. Estimates of total daily human exposure to benzo(j,k)fluorene are as follows (U.S.EPA, 1980a):

Source	Estimated Exposure (mg/day)
Water	0.017
Food	1.6-16
Air	0.040-0.080

These data indicate that food is the greatest source of benzo(j,k)fluorene. Pertinent exposure data for fluorene could not be located in the available literature.

2. ABSORPTION FACTORS IN HUMAN AND EXPERIMENTAL ANIMALS

Pertinent data regarding the absorption of fluorene or benzo(j,k)-fluorene following oral or inhalation exposure could not be located in the available literature. The relatively high lipid solubility of both compounds indicates that they are likely to be absorbed following oral or inhalation exposure.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

Pertinent data regarding subchronic, chronic, teratogenic or other reproductive effects of fluorene or benzo(j,k)fluorene following oral or inhalation exposure could not be located in the available literature.

Mixtures of polynuclear aromatic hydrocarbons, including benzo(j,k)-fluorene, have been tested for their interactive toxic effects in mice by subcutaneous exposure (Pfeiffer, 1973, 1977) and by dermal application (Schmahl et al., 1977). No synergistic or antagonistic effects were noted by either exposure method.

4. CARCINOGENICITY

Pertinent data regarding the carcinogenic potential of fluorene or benzo(j,k)fluorene in humans or laboratory animals by either the oral or inhalation routes of exposure could not be located in the available literature.

4.1. OTHER RELEVANT DATA

Horton and Christian (1974) made bi-weekly applications of benzo(j,k)-fluorene in decalin or in a 1:1 mixture (by volume) of decalin and the cocarcinogen n-dodecane to the interscapular skin of 15-20 two-month-old C3H male mice. The mice received 50/mg application and were treated for 82 weeks. No skin tumors were observed in mice treated with benzo(j,k)fluorene in either decalin or the decalin-n-dodecane mixture.

Van Duurren and Goldschmidt (1976) tested benzo(j,k)fluorene for its tumor promoting and cocarcinogenic activity. In the tumor promoting study, benzo(a)pyrene (150 mg) was applied to the skin of 50 female ZCR/Ha Swiss mice (6-8 weeks of age). Fourteen days after the benzo(a)pyrene application, benzo(j,k)fluorene in acetone at 40 mg was applied 3 times/week for the duration of the study (440 days). In this system, benzo(j,k)fluorene showed no tumor-promoting activity.

In the cocarcinogenicity study (Van Duuren and Goldschmidt, 1976), benzo(a)pyrene (5 mg) was applied to the skin of mice simultaneously with benzo(j,k)fluorene (50 mg) in acetone. The compounds were applied 3 times/week over a test period of 440 days. The number of mice with papillomas and carcinomas more than doubled with benzo(j,k)fluorene as compared with benzo-(a)pyrene controls (16/50 benzo(a)pyrene; 39/50 benzo(a)pyrene + benzo(j,k)-fluorene). Benzo(j,k)fluorene also increased the number of tumors per mouse

and decreased the days to the appearance of the first tumor as compared with the benzo(a)pyrene controls (210 days to first tumor, benzo(a)pyrene; 99 days, benzo(a)pyrene + benzo(j,k)fluorene).

Rice et al. (1984) applied [^{3}H]-benzo(a)pyrene (15-22 nmol=3.8-5.5 µg) in acetone or a mixture of [^{3}H]-benzo(a)pyrene (3.8-5.5 µg) and benzo(j,k)fluorene (37 µg) in acetone to the skin of 5-10 female CD-1 mice. After 24 hours, the mice were killed and the treated skin removed and analyzed for DNA adducts, evidence of DNA disruption. Co-application of benzo(j,k)fluorene with [^{3}H]-benzo(a)pyrene resulted in an average increase of DNA adduct formation of 66% as compared with [^{3}H]-benzo(a)-pyrene treatment alone.

A study by Busby et al. (1984) provides evidence that benzo(j,k)fluorene has activity as a complete carcinogen. In the mouse lung adenoma bioassay, at least 50 Swiss-Webster BLU:Ha newborn male and female mice were injected intraperitoneally with 1/7 of the dose on day 1, 2/7 of the dose on day 8 and the remaining 4/7 of the dose on day 15. Vehicle control mice received DMSO; positive control mice received benzo(a)pyrene; and the benzo(j,k)-fluorene-treated mice received a total dose of 700 µg (163 µg/kg) or 3.5 mg (815 mg/kg). At 24 weeks of age, treated mice were sacrificed, gross observations were recorded and lungs were fixed for histopathological examination.

The results showed that the 3.5 mg dose of benzo(j,k)fluorene induced a significant increase in the total incidence (58%, $p<0.0001$) and number of lung tumors (1.08 tumors/mouse, $p<0.001$) as compared with vehicle controls (9%, 0.09 tumors/mouse). About 20% of the mice with lung tumors in the high dose benzo(j,k)fluorene group had lesions diagnosed as adenocarcinomas. No

significant tumor response was observed in mice receiving the low benzo-(j,k)fluorene dose (20%, 0.24 tumors/mouse). None of the lung tumors in this group were diagnosed as adenocarcinomas. Positive controls responded appropriately.

Benzo(j,k)fluorene has been shown to be weakly mutagenic in Salmonella typhimurium strains TA100 (Kinae et al., 1981) and TA98 (Epler et al., 1978) with S-9 metabolic activation. Benzo(j,k)fluorene was found to be mutagenic in S. typhimurium strain TM677 with S-9 metabolic activation (Kaden et al., 1979). Kinae et al. (1981) observed negative results with benzo(j,k)-fluorene in S. typhimurium strains TA98 and TA1535 with or without metabolic activation and in the Bacillus subtilis rec assay.

Benzo(j,k)fluorene was negative for unscheduled DNA synthesis in the hepatocyte primary culture/DNA repair test (McQueen and Williams, 1980). The compound was also negative for gene mutation in the human lymphoblast line AHH-1, which is competent for xenobiotic metabolism (Crespi and Thilly, 1984).

Li (1984) determined benzo(j,k)fluorene to be weakly mutagenic in the CHO cell HGPRT assay with S-9 metabolic activation. The number of mutants was found to increase with the amount of S-9 added to the culture, although cell survival was reduced at higher S-9 concentrations. Benzo(j,k)fluorene was also mutagenic in repair-deficient CHO cells in the presence of rat microsomes at 0.5-0.7 mg/mℓ (Hoy et al., 1984).

Pertinent data regarding the carcinogenic potential of fluorene in laboratory animals by any route could not be located in the available literature. Fluorene has tested negative in mutation assays with S-9 metabolic activation using S. typhimurium strains TA98, TA100, TA1535 and TA1537 (Sakai et al., 1985; Epler et al., 1978; McCann et al., 1975).

Fluorene also was negative in the Escherichia coli WP2/WP100 rec assay (Mamber et al., 1983). The compound was found to be weakly mutagenic when tested with S. typhimurium strain TA97 with S-9 metabolic activation (Sakai et al., 1985).

Fluorene has also been tested in L517847K$^{+/-}$ mouse lymphoma cells for forward mutation (Oberly et al., 1984), in Chinese hamster cells for SCE in bone marrow (Neal and Probst, 1983), in negative primary culture/DNA repair assays using mouse and hamster hepatocytes (McQueen et al., 1983) and in the CHO/HGPRT assay (Hsie et al., 1979). In all the above tests, fluorene was negative.

4.2. WEIGHT OF EVIDENCE

Benzo(j,k)fluorene has been shown to have a potential to be a complete carcinogen in a newborn mouse lung adenoma bioassay (Busby et al., 1984). This evidence is sufficient to classify benzo(j,k)fluorene as an IARC Group 3 chemical and place it in EPA Group C, "possible human carcinogen" (U.S. EPA, 1986).

Because of the lack of studies concerning the carcinogenic potential of fluorene, it can be classified as an IARC Group 3 chemical and a EPA Group D chemical, "not classified" (U.S. EPA, 1986).

5. REGULATORY STANDARDS AND CRITERIA

An ambient water quality criterion of 42 µg/ℓ has been calculated for benzo(j,k)fluorene (U.S. EPA, 1980a). This value was derived from a study by Hoffmann et al. (1972) in which 50 µℓ of 1.0% benzo(j,k)fluorene applied to the skin of Swiss albino mice 3 times/week for 12 months caused no increase in mortality. Other parameters of toxicity were not evaluated. It is uncertain whether this value protects against the carcinogenic potential of benzo(j,k)fluorene.

No standards or criteria are available for fluorene.

6. RECOMMENDATIONS

Because of the lack of data for the carcinogenicity and threshold toxicity of benzo(j,k)fluorene and fluorene by relevant routes of exposure, risk assessment values for these compounds have not been derived in past health assessment activities. An ambient water quality criterion of 42 µg/ℓ was developed for benzo(j,k)fluorene (U.S. EPA, 1980a), based on the lack of increased evidence of mortality in mice dermally exposed 3 times/week for 12 months (Hoffmann et al., 1972). This study is insufficient for derivations of RfD/RfD_S values because the parameters of toxicity evaluated were not sufficient for estimation of a threshold for noncarcinogenic toxicity.

The primary issue requiring resolution is the carcinogenicity of fluorene and benzo(j,k)fluorene by oral or inhalation exposure. According to exposure data provided by the U.S. EPA (1980a), both routes of exposure may be important, at least for benzo(j,k)fluorene. Human data could not be located regarding the carcinogenicity of fluorene or benzo(j,k)fluorene and no animal data were located on fluorene. Fluorene was negative in mutagenicity tests in microorganisms (Mamber et al., 1983; Sakai et al., 1985) and in mutagenicity and clastogenicity tests in mammalian systems (Oberly et al., 1984; Neal and Probst, 1983; McQueen et al., 1983; Hsie et al., 1979). Benzo(j,k)fluorene, on the other hand, has been shown to be a cocarcinogen with benzo(a)pyrene in a dermal test in mice (Van Duuren and Goldschmidt, 1976), a complete carcinogen in the newborn mouse lung adenoma assay (Busby et al., 1984) and weakly mutagenic in prokaryotic (Kinae et al., 1981; Kaden et al., 1979) and mammalian (Li, 1984; Hoy et al., 1984) test systems.

These data, coupled with the fact tnat other polycyclic aromatic hydrocarbons are known carcinogens, emphasize the need to ascertain the carcinogenicity of fluorene and benzo(j,k)fluorene by oral and inhalation routes of exposure.

If adequate testing determines that these compounds are not carcinogenic, efforts should be made to determine thresholds for noncarcinogenic toxicity. Data are needed to determine the target organ(s) or system(s) most likely to be injured by exposure to these compounds. Oral exposure to determine subchronic, developmental and reproductive toxicity would also be necessary. Inhalation toxicity would be more difficult to ascertain because these compounds have relatively low vapor pressures (Mackay and Shui, 1981) and occur in the atmosphere largely associated with particulate matter.

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